

EDITORIAL COMMENT

Atheroma Volume by Intravascular Ultrasound as a Surrogate for Clinical End Points*

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Large-scale clinical studies have proven that primary and secondary prevention are effective methods in reducing myocardial infarction, stroke, and overall mortality. An unresolved issue is the optimal levels of lipids and blood pressure to achieve these goals (1,2). National treatment guidelines have progressively lowered thresholds for treatment initiation and target levels (3,4). Although the recent trend has been that “lower is better,” the ideal targets for low-density lipoprotein cholesterol (LDL-C) and blood pressure, and the interaction between these 2 parameters, have not been clearly defined.

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In this issue of the *Journal*, Chhatriwalla et al. (5) attempt to clarify the relationship between levels of LDL-C and systolic blood pressure and their effects on coronary plaque progression. The study incorporated 3,437 patients with established coronary artery disease who were enrolled in 7 clinical trials that were stratified into 4 groups according to blood pressure and LDL-C levels. Changes in atheroma burden were monitored by serial intravascular ultrasound (IVUS), which was performed at baseline and at 18 to 24 months with the use of standard parameters. The subgroup with very low LDL-C (≤ 70 mg/dl) and normal systolic blood pressure (SBP) (≤ 120 mm Hg) displayed the least progression in percent atheroma volume (PAV) and total atheroma volume (TAV) ($p < 0.001$ for trend). This group also displayed more frequent plaque regression ($p < 0.01$) compared with other subgroups. In patients with SBP > 120 mm Hg, very low LDL-C was still associated with less progression of PAV, whereas in the group with LDL-C

> 70 mg/dl, normal SBP was not associated with less progression of PAV or TAV. These observations suggest that lipid lowering may have a larger impact on plaque progression compared with blood pressure lowering, which is consistent with previous findings (6).

This study complements the recent SANDS (Stop Atherosclerosis in Native Diabetics Study) trial (7), where 499 patients with type 2 diabetes were randomized to aggressive (goal LDL-C ≤ 70 mg/dl, SBP ≤ 115 mm Hg) versus standard (goal LDL-C ≤ 100 mg/dl, SBP ≤ 130 mm Hg) medical therapy and were evaluated by common carotid artery intimal medial thickness during the course of 36 months. Mean levels (95% confidence interval) for LDL-C were 72 and 104 mg/dl, and SBP levels were 117 and 129 mm Hg in aggressive versus standard groups, respectively.

Compared with baseline, mean intimal medial thickness regressed in the aggressive group and progressed in the standard group (-0.012 mm vs. 0.038 mm; $p < 0.001$). It is becoming increasingly clear from animal and human data that a combination of aggressive lipid-lowering and blood pressure control may be necessary for maximum attenuation of plaque progression (8,9), improvement in endothelial function (10,11), and reduced plasma level markers of inflammation of oxidative stress (12).

Chhatriwalla et al. (5) provide an interesting commentary on the need for more aggressive treatment guidelines for “pre-hypertension,” that is, blood pressure of 120 to 139/80 to 89 mm Hg in patients with established coronary artery disease. Prehypertension has been associated with increased event rates (13) and is under-recognized and undertreated. The lack of large, randomized trials with hard clinical end points have likely contributed to a delayed acceptance of the need for pharmacological treatment in these individuals. SPRINT (Systolic Blood Pressure Intervention Trial) is a randomized multicenter trial that will compare intensive (SBP < 120 mm Hg) versus standard (SBP < 140 mm Hg) blood pressure control in patients older than 55 years of age with an SBP > 130 mm Hg and at least 1 other cardiovascular disease (CVD) risk factor. The study will focus on high-risk patients, such as those with clinical cardiovascular disease (not including stroke), patients with stage 3 kidney disease, and patients without clinical CVD who have other CVD risk factors such as low high-density lipoprotein (HDL). Primary composite end points will include CVD mortality, nonfatal myocardial infarction, stroke, and heart failure. The results of this highly anticipated trial may have a profound influence on how prehypertension is prioritized.

Chhatriwalla et al. (5) use IVUS measurements of atheroma volume as a surrogate end point in place of clinical events. As distinguished from angiography, which provides a 2-dimensional longitudinal image of the artery lumen, IVUS uses high-frequency soundwaves to reveal the atherosclerotic plaque deposited within the arterial wall. The use of IVUS provides low-resolution, cross-sectional images of coronary arteries and is useful because it produces an image

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in a living person, usually attainable only with histology from autopsy specimens.

In the REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid Lowering) (14) and ASTROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) (15) trials, authors used IVUS to demonstrate that aggressive lipid management was associated with slower plaque progression and even plaque regression in patients with known coronary artery disease (CAD). In REVERSAL, 80 mg/day of atorvastatin was compared with 40 mg/day of pravastatin in 654 patients with angiographically established CAD who underwent IVUS at baseline and at 18 months. For the primary end point of percent change in TAV, a significantly lower rate of progression from baseline was observed in the atorvastatin group (-0.4%) as compared with the pravastatin group (2.7% , $p = 0.02$). The ASTROID trial evaluated the effect of maximally intensive statin therapy with 40 mg/day of rosuvastatin in 349 patients with CAD. The IVUS measurements performed at baseline and at 24 months demonstrated a reduction of total plaque volume by 6.8% ($-14.7 \pm 25.7 \text{ mm}^3$) ($p < 0.001$). The medication intervention trials published by this IVUS core laboratory (16–19) are a product of a monumental amount of effort and 10 years of development and have contributed impressively to our knowledge and understanding of pharmacological therapies for atherosclerosis.

We must exercise caution, however, when interpreting studies that use atheroma burden measured by IVUS as a surrogate end point. The acceptance of this parameter is largely based on evidence that luminal narrowing (20) or plaque progression (21) on IVUS in the left main artery at one specific cross section has been associated with future coronary events in patients with CAD and in the left anterior descending artery in patients undergoing heart transplant (22). However, the interpretation of trials with the use of IVUS as a surrogate end point must be placed into perspective: IVUS, although a robust clinical and research tool, is subject to certain limitations.

In the aforementioned clinical studies, atheroma volume is obtained by taking the sum of the differences between external elastic membrane (EEM) cross-sectional area and the luminal cross-sectional area for all available images. TAV is then obtained by first calculating the mean cross-sectional atheroma area for each pullback study. This area is then indexed by multiplying by the average length of the entire population of IVUS exams. To our knowledge, this method of calculating TAV, although logical, has never been directly correlated with clinical event rates even within these clinical trials because they were not powered for clinical events. Additionally, there are several sources of potential error when acquiring these data from intravascular ultrasound.

Any obstruction or distortion of the border of the EEM or lumen can contribute to measurement error and decrease reproducibility. For example, significant artifacts can be

created by regions of heavy calcification, causing one difficulty in defining the EEM border. Nonuniform rotational distortion, a phenomenon created by variations in catheter rotation speeds; transducer ring down, a result of acoustic oscillations resulting in high frequency signals that obscure near field imaging; and geometric distortion, which occurs when the ultrasound beam interrogates a plane that is not orthogonal to vessel walls, can obscure an operator's ability to define the true luminal and EEM borders.

Additionally, variations in pullback speeds between the baseline and follow-up measurements can interfere with the calculation of total atheroma volumes. These limitations can be corrected mathematically when there is a known length of artery, for example, if one is evaluating intimal hyperplasia within coronary stents. The pullback length from the baseline and follow-up IVUS can be indexed to the known length of the stent. It is less certain that we can do this accurately when calculating atheroma volume from 2 separate studies where the average difference in pullback length may be 10% between anatomic landmarks. The scientific community could be reassured of the accuracy of this method by having an independent IVUS Core Lab repeat the analysis of these data.

Although we may use plaque progression/regression on IVUS to deduce that we are producing positive results for our patients, the true determination of the impact of our therapy depends on clinical and mortality end points, which can only be obtained from large-scale randomized clinical trials. It must be recognized that a direct relationship between atheroma progression and regression on IVUS and hard clinical events has never been clearly defined. For example, it is possible that a greater clinical effect is produced by altering plaque composition from lipid-rich to more fibrotic tissue, thus stabilizing the atheroma, independent of any change in lumen area or plaque volume. Therefore, until clinical outcomes are shown to correspond with predictions based on the IVUS surrogates, conclusions derived from these trials should be considered inferential, to be used as guides for future trials focused on clinical outcome measures.

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REFERENCES

1. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol* 2006;48:438–45.
2. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–13.
3. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–97.

4. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206–52.
5. Chhatriwalla AK, Nicholls SJ, Wang TH, et al. Low levels of low-density lipoprotein cholesterol and blood pressure and progression of coronary atherosclerosis. *J Am Coll Cardiol* 2009;53:1110–5.
6. Teo KK, Burton JR, Buller CE, et al. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation* 2000;102:1748–54.
7. Howard BV, Roman MJ, Devereux RB, et al. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. *JAMA* 2008;299:1678–89.
8. Kato M, Sada T, Mizuno M, Kitayama K, Inaba T, Koike H. Effect of combined treatment with an angiotensin II receptor antagonist and an HMG-CoA reductase inhibitor on atherosclerosis in genetically hyperlipidemic rabbits. *J Cardiovasc Pharmacol* 2005;46:556–62.
9. Trion A, de Maat M, Jukema W, et al. Anti-atherosclerotic effect of amlodipine, alone and in combination with atorvastatin, in APOE*3-Leiden/hCRP transgenic mice. *J Cardiovasc Pharmacol* 2006;47:89–95.
10. Ceriello A, Assaloni R, Da Ros R, et al. Effect of atorvastatin and irbesartan, alone and in combination, on postprandial endothelial dysfunction, oxidative stress, and inflammation in type 2 diabetic patients. *Circulation* 2005;111:2518–24.
11. Koh KK, Quon MJ, Han SH, et al. Vascular and metabolic effects of combined therapy with ramipril and simvastatin in patients with type 2 diabetes. *Hypertension* 2005;45:1088–93.
12. Koh KK, Quon MJ, Han SH, Ahn JY, Lee Y, Shin EK. Combined therapy with ramipril and simvastatin has beneficial additive effects on tissue factor activity and prothrombin fragment 1+2 in patients with type 2 diabetes. *Atherosclerosis* 2007;194:230–7.
13. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. *JAMA* 2005;294:466–72.
14. Nissen SE. Halting the progression of atherosclerosis with intensive lipid lowering: results from the Reversal of Atherosclerosis With Aggressive Lipid Lowering (REVERSAL) trial. *Am J Med* 2005;118:22S–7S.
15. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006;295:1556–65.
16. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA* 2003;290:2292–300.
17. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA* 2004;292:2217–25.
18. Nissen SE, Tardif JC, Nicholls SJ, et al. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med* 2007;356:1304–16.
19. Nissen SE, Nicholls SJ, Wolski K, et al. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease. *JAMA* 2008;299:1547–60.
20. Ricciardi MJ, Meyers S, Choi K, Pang JL, Goodreau L, Davidson CJ. Angiographically silent left main disease detected by intravascular ultrasound: a marker for future adverse cardiac events. *Am Heart J* 2003;146:507–12.
21. Von Birgelen C, Hartmann M, Mintz GS, et al. Relationship between cardiovascular risk as predicted by established risk scores versus plaque progression as measured by serial intravascular ultrasound in left main coronary arteries. *Circulation* 2004;110:1579–85.
22. Kobashigawa JA, Tobis JM, Starling RC, et al. Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years. *J Am Coll Cardiol* 2005;45:1532–7.

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